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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/009,846	01/20/1998	ROBERT ZAMBIAS	5925-061-999	7948

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PENNIE & EDMONDS
1155 AVENUE OF THE AMERICAS
NEW YORK, NY 100362711

EXAMINER

PONNALURI, PADMASHRI

ART UNIT

PAPER NUMBER

1627

DATE MAILED: 08/16/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

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Office Action Summary

Application No.

09/009,846

Applicant(s)

Zambias et al

Examiner

Padmashri Ponnaluri

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 8/9/02 and 5/28/02.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 10-13, 17, 18, 22-24, and 26 is/are pending in the application.
- 4a) Of the above, claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 10-13, 17, 18, 22-24, and 26 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
*See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____ 6) ☐ Other:

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DETAILED ACTION

1. A request for continued examination under 37 CAR 1.114, including the fee set forth in 37 CAR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CAR 1.114, and the fee set forth in 37 CAR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CAR 1.114. Applicant's submission filed on 5/28/02 has been entered.
2. The preliminary amendment I, filed on 5/2/02 has been fully considered and entered into the application.
3. The preliminary amendment J, filed on 8/12/02 has been fully considered and entered into the application.
4. The amendment H, filed on 10/25/01 has been fully considered and entered into the application.
5. New claim 26 has been entered by the amendment J, filed on 8/12/02.
6. Claims 20-21 and 25 have been canceled by the amendment H, filed on 10/25/01.
7. Claims 10-13, 17-18, 22-24 and 26 are currently pending and are being examined in this application.
8. The 35 U. S. C. . 112, second paragraph rejections of claims 20-21 and 25 have been withdrawn in view of applicants cancellation of claims.

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9. The petition under 37 CAR 1.47(a) filed on 4/20/00 has been fully considered and granted in this application. The objection to the oath/declaration as defective set forth in the previous office action has been withdrawn in view of the granted petition.

10. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CAR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

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12. Claims 10-13, 17-18 and 20-26 (NOTE CLAIM 26 IS NEW) rejected under 35 U.S.C. 103(a) as being unpatentable over Pirrung et al (Advance ACS Abstract, vol. 8, No. 1, January 1, 1995) and Gallop et al (Journal of Medicinal Chemistry, vol. 37, No. 9, April 29, 1994, pages 1233-1251).

Pirrung et al teach a method for preparation and screening against acetylcholine esterase of a non-peptide "indexed" combinatorial library. The reference teaches a combinatorial library composed from nine alcohols and six isocyanates (refers to compounds of the instant claims) to formally generate 54 carbomates. The reference teaches to deduce most active member of the library, it was prepared as 15 sublibraries (refers to sub arrays of the instant claims) in which one of the reacting component was fixed (refers to molecular core of the instant claims) and the other reactant used in equimolar mixtures. The reference teaches that the product mixtures were tested and their activities used as indices to the rows and columns of a two dimensional matrix (refers to spatially addressable array of the instant claims) reflecting the actives of individual carbomates. The reference teaches that the indexed libraries offer the advantage that they can be prepared from any class of compounds composed of multiple subunits and that any class type of assay can be used because all compounds are generated in free form (refers to in solution of the instant claims).

The claimed invention differs from the prior art teachings by reciting combinatorial array of at least 500 different compounds. Pirrung et al teach indexed combinatorial library, and the advantages of the indexed library. Pirrung et al do not teach 500 different compounds in the

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library. Gallop et al review combinatorial techniques and the screening methods. Gallop et al teach that depending on the number of individual compound sin a library (N) depends on the number of building blocks (b) (reactants) available for each step, and the number of reaction steps in reaction scheme (x), and $N = b^x$. i.e., the reference teaches that using 100 building blocks permits the theoretical synthesis of 100 million tetrameric chemical entities (page 1234, and figure 1). Thus, a combinatorial library of 500 different compounds can be prepared using the formula given by Gallop et al. Pirrung et al do not specifically teach the split synthesis. However, the split synthesis method is well known in the art. Gallop et al teach a method for preparation of a combinatorial library by the split synthesis method (see page 1242, and figure 2). Thus, it would have been obvious to a person skilled in the art at the time the invention was made to use the split method synthesis with indexed library synthesis method taught by Pirrung et al and use 500 different vessels to obtain 500 different compounds in the library, because Pirrung et al teach indexed libraries by preparing 15 different libraries, and Gallop et al teach a method for split synthesis and a method to determine the number of individual units in a library. A person skilled in the art would have been motivated to use the indexed library of Pirrung et al to synthesize a combinatorial library of 500 different compounds because Pirrung et al teach that the method can be prepared using any class of compounds and can be used for any type of assay because all compounds are generated in a free form.

New claim 26 has been included in this rejection because, the new claim is substantially same (in scope) as rejected claim 10. New claim 26 recites in step (a) providing at least 500 wells

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organized into at least first and second sub-arrays, which is not any different from the rejected claim 10 recitation of 'providing at least 500 vessels....'. Thus the rejections of record would read on new claim 26.

13. *Applicant's arguments filed on 10/25/01, regarding the art rejection of record (office action mailed on 4/25/01) have been fully considered but they are not persuasive.*

Applicants argue that the Pirrung reference does not teach Solution phase synthesis. *Applicants arguments have been considered but are not persuasive. Because the reference do not explicitly teach that the compounds are made by solution phase, however, the reference teaches that the compounds are 'free form', which means that the compounds are not attached to solid supports. That would mean that the compounds are in solution phase.*

Applicants further argue that the reference disclosure '...in which one of the reacting component is fixed.' has been fully considered and entered into the application but is not persuasive. Because in the reference disclosure 'in which one of the reacting component is fixed, applicants mean in each of the 15 libraries one of the component is same. It is not immobilized or attached to solid support as applicants argue. Applicants argue because reference discloses that '....in which one of the reacting component is fixed' the reference library is not solution is not persuasive.

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*In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, the Gallop et al reference (a review article) teaches that the chemical libraries are intentionally created collections of differing molecules which can be prepared either synthetically or biosynthetically and screened for biological activity in a variety of different formats (e.g., libraries of soluble molecules...). Thus the reference teaches that the combinatorial libraries can be made in solution phase. The reference in page 1234, (left column, first two paragraphs) teaches the use of building block approach to create 'chemical libraries', and teaches the reaction scheme. The reference during the discussion nowhere discusses that the building block approach is not useful in solution phase or it is useful only with solid phase synthesis. Thus, it would have been obvious to a person skilled in the art at the time the invention was made to combine the building block approach of Pirrung et al with the 'Indexed library' method taught by Pirrung et al to make an array of 500 different compounds. Applicants argue that the 'split synthesis' method taught by Gallop et al is solid phase synthesis which can not be combined with solution phase synthesis of Pirrung et al. Applicants arguments are not persuasive, because the 'split synthesis method' discussed by Gallop et al is a general method,*

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even though Gallop et al teach in reference to solid phase synthesis. The split synthesis method could be used for solution phase synthesis. The instant claimed method recites the reactions in test tubes or in wells, it is not clear how it would be different from the solid phase synthesis in which the reactants are attached to substrates and placed in vessels or tubes. Each test tube in the instant method could be equal to solid support of the split method. Applicants argue that the solid phase methods described by Gallop et al are not applicable to the solution phase methods of the instant methods. Applicants arguments are not persuasive. Applicants have not pointed out how the instant method compounds would be different from the reference (by not using the solid supports) during the synthesis, since the instant method compounds (reactants) are in the test tubes which would be equal to the compounds (reactants) attached to beads and placed in vessels taught by the reference. The compounds are in solution phase or attached to the solid supports would only make a difference during testing or screening. Since the solid phase bound compounds may not interact with the testing compound as freely as the solution phase or free form compounds. However, Pirrung et al teach solution phase method in synthesis of combinatorial library of compounds. Pirrung et al teach the advantages of the free form of compounds in a library. Gallop et al teach the solution phase method of combinatorial library. Gallop et al teach solid phase split pool synthesis method in synthesis of combinatorial library. Since Pirrung et al teach the advantages of the solution phase synthesis and Gallop et al teach solution phase synthesis, it would be obvious to one skilled in the art to combine the teachings of

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split pool synthesis method taught by Gallop et al with the solution phase synthesis taught by Pirrung et al The rejections have been maintained for the reasons of record.

14. No claims are allowed.

15. All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CAR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CAR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CAR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CAR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CAR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the mailing date of this final action.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to P. Ponnaluri whose telephone number is (703) 305-3884. The examiner is on *Increased Flex Schedule* and can normally be reached on Monday to Friday from 7.00 AM to 3.30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Mckane, can be reached on (703) 308-4537. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

P. Ponnaluri
Patent Examiner
Technology Center 1600
Art Unit 1627
14 August 2002


PADMASIRI PONNALURI
PRIMARY EXAMINER